CLINICAL SCIENCES

SYNOVIAL SARCOMA OF THE EXTREMITIES: PROGNOSTIC FACTORS FOR 20 NONMETASTATIC CASES AND A NEW HISTOLOGIC GRADING SYSTEM WITH PROGNOSTIC SIGNIFICANCE

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Baptista AM, Camargo OP de, Croci AT, Oliveira CRGCM de, Azevedo Neto RS de, Giannotti MA et al. Synovial Sarcoma Of The Extremities: Prognostic Factors For 20 Nonmetastatic Cases And A New Histologic Grading System With Prognostic Significance. CLINICS. 2006;61(5):381-6.

PURPOSE: To evaluate 20 cases of nonmetastatic synovial sarcoma of the extremities regarding prognostic factors, and to propose a histologic grading system with prognostic significance.
METHODS: The cases of 20 patients (14 females and 6 males) with nonmetastatic synovial sarcomas of the extremities treated between 1985 and 1998, were retrospectively evaluated regarding prognostic factors. A histologic grading system with prognostic significance is proposed.
RESULTS: The mean follow-up period was 48.4 months (range, 16-116 months). There was local recurrence in 3 cases (15%), microscopic surgical margin being the only prognostic factor identified. Seven patients (35%) died of the disease in a mean postoperative period of 31.7 months (range, 16-53 months), all with pulmonary or brain metastasis. The survival rate was 65% in 48.4 months of follow-up.
CONCLUSION: The unfavorable prognostic factors identified regarding survival were high histologic grade, tumors proximal to the knee or elbow, and spontaneous tumor necrosis over 25%. Local recurrence did not have influence on survival in this study. The presence of mast cells appears to have a positive influence on survival, although statistical significance was not reached (P = 0.07). The oncologic and functional result was good in 6 cases (30%), regular in 7 (35%), and poor in 7 cases (35%).

KEYWORDS: Synovial, sarcoma. Extremities. Retrospective studies. Prognosis. Soft tissue neoplasms.

INTRODUCTION

Synovial sarcoma (SS) is the fourth most common soft tissue sarcoma,[1] after malignant fibrous histiocytoma, liposarcoma, and rhabdomyosarcoma. It is more prevalent in males (1.2:1) between 15 and 40 years of age. About 75% of the cases of SS arise in the extremities, especially in the lower extremity, and there are 4 histologic subtypes described: biphasic, monophasic fibrous, monophasic epithelial, and poorly differentiated. Five-year survival rates range from 30% to 74%,[2,3] and several prognostic factors have been described.

Most pathologists consider the SS a high-grade sarcoma, independent of its histologic characteristics. Nevertheless, some authors have tried to identify high- and low-risk groups, as well as prognostic factors regarding survival and local recurrence.

The objective of this study was to identify the prognostic factors regarding survival and local recurrence in 20 cases of SS of the extremities treated in a single institu-

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tion. A histologic grading system with prognostic significance is proposed, dividing the tumors among low and high histologic grades.

MATERIALS AND METHODS

From 1950 to 1998, the Orthopedic Oncology Group of the Department of Orthopedics treated 351 patients with a diagnosis of soft-tissue sarcomas. Among them, 87 were SS, and 20 of them had complete data and were selected for this study. All patients underwent surgery, with 5 of them also undergoing radiation therapy and 1 undergoing chemotherapy postoperatively. There was no neoadjuvant therapy in this study.

The case index number, as well as age, gender, anatomic site, and date of the surgery are listed on Table 1.

Table 1 - Patients distributed according to age, gender, anatomic site, and date of surgery

Nº	AGE	GENDER	ANATOMIC SITE	DATE OF SURGERY
1	45	Female	Right Wrist	Dec / 1985
2	29	Male	Right Ankle	Oct / 1989
3	18	Female	Right Ankle	Dec / 1989
4	17	Female	Right Thigh	Jul / 1991
5	23	Female	Right Forearm	Jan / 1992
6	23	Female	Left Leg	Jun / 1993
7	41	Female	Left Ankle	Sep / 1993
8	42	Female	Left Arm	Oct / 1993
9	45	Male	Left Thigh	Aug / 1994
10	13	Female	Right Wrist	May / 1995
11	31	Male	Left 3rd toe	Jun / 1996
12	38	Female	Right Knee	Jul / 1996
13	20	Female	Right Arm	Aug / 1996
14	31	Female	Right Thigh	Nov / 1996
15	25	Male	Left Arm	Nov / 1996
16	11	Male	Right Foot	Jun / 1997
17	26	Female	Left Foot	Oct / 1997
18	24	Male	Right Thigh	Nov / 1997
19	11	Female	Right 2nd Finger	Dec / 1997
20	36	Female	Left Foot	Jan / 1998

The inclusion criteria for this study were as follows: 1) histologic diagnosis of SS, 2) anatomic site in the extremities, 3) no evidence of metastasis on chest CT scan, and 4) a minimum follow-up of 24 months for the surviving patients.

The chest CT scan was used for the detection of lung metastasis, the most common site among soft-tissue sarcomas.

The average age was 27.4 years (range, 11-45 years), and there were 14 females and 6 males. All cases were at least partially deep tumors, with 7 occurring in the upper extremity and 13 in the lower extremity. Nine cases were proximal to the knee or the elbow, and 11 cases were distal. Thirteen patients had tumors smaller than 10 cm, and 7 had tumors 10 cm or more at the longest axis. We chose the criterion, smaller and larger than 10 cm, because the mean size of the tumors in our study was 9.3 cm. Conventional radiographs and MRI of the tumor were made, as well as were chest radiographs and chest CT scans. Biopsy was percutaneous in all cases.

All patients underwent surgery, with 12 wide resections and 8 amputations.

The anatomopathologic study was made using hematoxylin-eosin stain, as well as an immunohistochemistry study to confirm the diagnosis of SS. The monoclonal antibodies used were vimentin, keratin, EMA, actin, enolase, and S-100. Reticulin stain was used when the epithelial pattern was not evident.

The following 10 histologic variables were evaluated: microscopic surgical margin, histologic subtype, mitotic rate, glandularity, spontaneous necrosis, presence of calcifications, hyalinization, presence of mast cells, presence of a hemangiopericytic pattern, and presence of rhabdoid cells (Table 2).

Table 2 - Patients distributed according to histologic variables

Histologic variable		Number of patients
Microscopic surgical margin	Negative	16
	Positive	4
Histologic subtype	Biphasic	4
	Monophasic fibrous	14
	Monophasic epithelial	0
	Poorly differentiated	2
Mitotic Rate	< 5 mitosis / 10 HPF	8
	≥ 5 mitosis / 10 HPF	12
Glandularity	< 50%	16
	≥ 50%	4
Spontaneous necrosis	≤ 25%	13
	> 25%	7
Calcification or ossification	Present	7
	Absent	13
Hyalinization	Low	14
	Moderate / Accentuated	6
Mast cells	Present	9
	Absent	11
Hemangiopericytic pattern	Present	11
	Absent	9
Rhabdoid cells	Present	1
	Absent	19

The histologic grading system proposed considered high-grade tumors those with a mitotic rate of 5 or more mitosis figures in 10 high-power fields (HPF), more than 25% spontaneous necrosis, and less than 50% glandularity. Seven patients fulfilled these criteria. The remaining 13 cases were considered low-grade tumors.

All the above mentioned variables were studied regarding local recurrence and disease-related survival.

The oncologic and functional result was considered (i) good when the patient was alive with no evidence of disease (NED) after undergoing a limb-salvage procedure, (ii) medium when alive with NED but having undergone amputation, and (iii) poor when the patient died of the disease (DOD) or was alive with disease (AWD).

A statistical analysis was performed using the 2-tailed Fisher exact test, with 5% as the significance index (P = 0.05). The Kaplan-Meier method was used to estimate the survival and local recurrence rates during the follow-up period.[4]

RESULTS

The overall mean follow-up was 48.4 months (range, 16-116 months). Among the living patients at the last evaluation, the mean follow-up was 57.5 months (24-116). No patients were lost to follow-up.

Local recurrence

Four patients presented initially as having recurrences (Table 3). After surgery, 3 patients developed a local recurrence, with one of them being 1 of the 4 patients who presented with recurrence. Figure 1 illustrates the occurrence of local recurrence during the follow-up period.

Survival

The overall survival was 65% in a mean follow-up period of 48.4 months. Seven patients died of the disease due to pulmonary metastases, one of them also having brain metastases (Table 4). Figure 2 illustrates the occurrence of disease-related death over the follow-up period.

The oncologic and functional result was good in 6 cases, medium in 7, and poor in 7 cases. There were no patients alive with disease; all individuals in the "poor" category died of the disease.

DISCUSSION

Efforts have been made in the last decades to establish prognostic factors for soft-tissue sarcomas (STS). Nonetheless, approximately 30 different histologic entities are classified as STS, many of them with different biologic behaviors. Malignant fibrous histiocytoma (MFH), for instance, has a different behavior when compared to SS. Due to the rarity of these lesions, many authors[2, 5-7 2,7,12,22] divide them between high- and low-grade sarcomas, thus

Table 3 - Local recurrence according to all variables

Variable		Local recurrence	*P*
Sex	Female	3 / 14	0.521
	Male	0 / 6	
Age	≤ 20	1 / 6	1.000
	> 20	2 / 14	
Size	< 10 cm	3 / 13	0.521
	≥ 10 cm	0 / 7	
Limb	Upper	2 / 7	0.270
	Lower	1 / 13	
Location	Proximal	1 / 9	1.000
	Distal	2 / 11	
Status at presentation	Primary	2 / 16	0.509
	Recurrence	1 / 4	
Type of surgery	Resection	3 / 12	0.242
	Amputation	0 / 8	
Adjuvant radiation therapy	Used	2 / 5	0.140
	Not used	1 / 15	
Microscopic surgical margin	Clear	0 / 16	0.004 (*)
	Positive	3 / 4	
Histologic subtype	Monophasic fibrous	1 / 14	0.405
	Biphasic	1 / 4	
	Poorly differentiated	1 / 2	
	Monophasic epithelial	0 / 0	
Mitotic rate	< 5 mitosis / 10 HPF	1 / 8	1.000
	≥ 5 mitosis / 10 HPF	2 / 12	
Glandularity	< 50%	2 / 16	0.509
	≥ 50%	1 / 4	
Spontaneous necrosis	≤ 25%	2 / 13	1.000
	> 25%	1 / 7	
Calcification or ossification	Present	0 / 7	0.521
	Not present	3 / 13	
Hyalinization	Mild	3 / 14	0.521
	Moderate / Accent.	0 / 6	
Mast cells	Present	1 / 9	1.000
	Not present	2 / 11	
Hemangiopericytic pattern	Present	2 / 11	1.000
	Not present	1 / 9	
Rhabdoid cells	Present	0 / 1	1.000
	Not present	3 / 19	
Histologic grade	High	1 / 7	1.000
	Low	2 / 13	

(*) = statistically significant

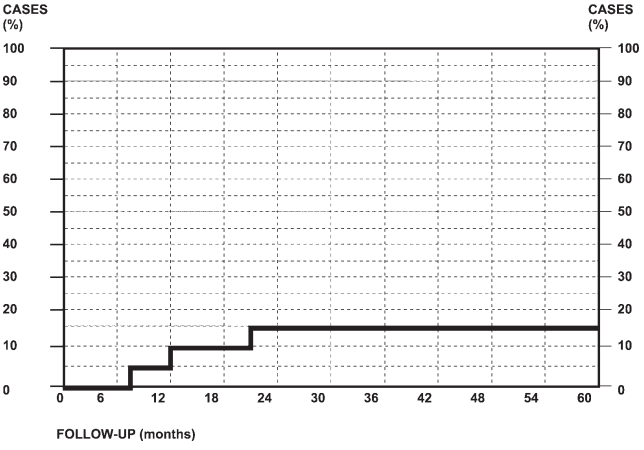

Figure 1 - Kaplan-Meier estimates for local recurrence

Table 4 - Disease-related survival according to all variables

Variable		DRD	*P*
Sex	Female	4 / 14	0.613
	Male	3 / 6	
Age	≤ 20	1 / 6	0.354
	> 20	6 / 14	
Size	< 10 cm	3 / 13	0.174
	≥ 10 cm	4 / 7	
Limb	Upper	4 / 7	0.174
	Lower	3 / 13	
Location	Proximal	6 / 9	0.017 (*)
	Distal	1 / 11	
Status at presentation	Primary	5 / 16	0.587
	Recurrence	2 / 4	
Type of surgery	Resection	4 / 12	1.000
	Amputation	3 / 8	
Adjuvant radiation therapy	Used	1 / 5	0.613
	Not used	6 / 15	
Local recurrence	Present #	2 / 6	1.000
	Not present	5 / 14	
Microscopic surgical margin	Clear	6 / 16	1.000
	Positive	1 / 4	
Histologic subtype	Monophasic fibrous	6 / 14	0.245
	Biphasic	0 / 4	
	Poorly differentiated	1 / 2	-
	Monophasic epithelial	0 / 0	-
Mitotic rate	< 5 mitosis / 10 HPF	1 / 8	0.158
	≥ 5 mitosis / 10 HPF	6 / 12	
Glandularity	< 50%	7 / 16	0.249
	≥ 50%	0 / 4	
Spontaneous necrosis	≤ 25%	2 / 13	0.022 (*)
	> 25%	5 / 7	
Calcification or ossification	Present	4 / 7	0.174
	Not present	3 / 13	
Hyalinization	Mild	4 / 14	0.613
	Moderate / Accent.	3 / 6	
Mast cells	Present	1 / 9	0.070
	Not present	6 / 11	
Hemangiopericytic pattern	Present	5 / 11	0.374
	Not present	2 / 9	
Rhabdoid cells	Present	0 / 1	1.000
	Not present	7 / 19	
Histologic grade	High	5 / 7	0.022 (*)
	Low	2 / 13	

= including recurrences at presentation
(*) = statistically significant DRD = disease-related death

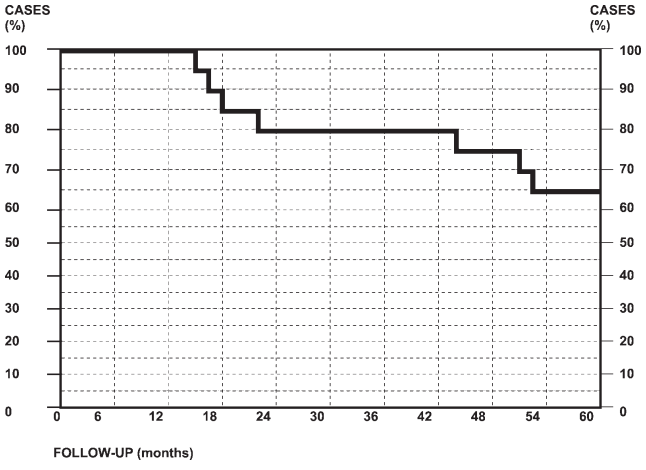

Figure 2 - Kaplan-Meier estimates for disease-related survival

achieving an adequate number of cases for statistical analysis. We believe it is not safe to generalize the conclusions of these studies. Multicentric studies of each tumor would probably be the best choice. The present study is part of an overall project of the Department to systematically review our records concerning the treatment of musculoskeletal tumors .[8-10] Despite improvements in staging, surgical technique, and adjuvant therapies, SS remains one of the most aggressive STS. Since 1936, when Knox[11 5] first used the term synovial sarcoma, the aggressiveness of this entity has been described. Five-year survival rates range from 30%[3] to 74%,[2] and the lungs are, as in most sarcomas, the most affected organ by metastases. Lymph node metastases are uncommon in sarcomas, but SS may present them more frequently than other tumors. We had 2 patients with positive regional lymph nodes in our study.

Several pathologists primarily consider SS a high-grade STS. Our impression, based on our experience, is that the biologic behavior in some cases is more benign than others. Thus the objective of separating the high-grade, more aggressive cases from the low-grade ones is to identify the more benign tumors that have better survival prognosis.

When considering local recurrence, our study showed that the only prognostic factor was the microscopic surgical margin. When it is positive, most of the cases recur. Several studies have identified this variable as prognostic in terms of local recurrence.[3,5,12,13 3,6-8] Many studies suggest that adjuvant radiation therapy has good influence in recurrence rates [6,14,15 9-12]. In fact, it is almost a consensus among orthopedic oncology surgeons that adjuvant radiation therapy diminishes the local recurrence rates in STS, especially in high-grade tumors. Some authors indicate radiation therapy in high grade STSs larger than 5 cm, others in recurrent cases, and some preoperatively in tumors near neurovascular bundles. The indications vary, but most authors agree that radiation therapy lowers the chances of local recurrence. Nevertheless, serious complications may occur after radiation therapy, especially external beam radiation. These include dehiscence, limb length discrepancy in children, avascular necrosis, and pathologic fracture. [6,16 11,12] We did not have enough data to evaluate this issue. It is interesting to observe, though, that local recurrence did not worsen the survival prognosis in our study. As other authors previously described, the influence of local recurrence on survival remains controversial. [17 13] Some authors believe that patients that present with local recurrence have a poorer survival prognosis. [17-19 13-15] Others believe, as we do, that local recurrence does not influence survival.[12, 20, 21 6,16,17]

Regarding survival, the unfavorable prognostic factors identified in our study were spontaneous necrosis over 25%,

tumors proximal to knee or elbow, and high histologic grade tumors according to our criteria.

Some investigators have tried to establish high- and low-risk groups based on histologic variables. Skitting et al. [22] [18] defined as favorable cases those presenting cellular atypia, no necrosis and a mitotic rate under 10/10 HPF. These cases had a survival rate of 83%, whereas the remaining patients had only a 31% survival rate. Our criteria, although slightly different, present similar results. We defined high-grade tumors as those showing mitotic rate of 5 or more per 10 HPF, more than 25% of spontaneous necrosis, and less than 50% of glandularity. The remaining cases were considered low-grade cases. Patients with low-grade tumors had a 71% survival rate, compared to those with high-grade tumors, who had a 15% survival rate.

In most studies, proximal location is usually not an unfavorable prognostic factor. In our series, however, patients with proximal tumors had a survival rate of 33%, versus a survival rate of 91% for those with distal tumors. Mullen and Zagars[6] [12] and Hadju et al[23] [19] also had similar results.

Several prognostic factors have been described as significant for survival in SS, including primary size of the tumor, margin of resection, and histologic subtype. Size is one of the most described prognostic factors. Patients with tumors smaller than 5 cm had better survival prognoses in several studies. [2,6,7,13,17,20,24-28] [2,8,12,13,16,20-25] Our study, despite a tendency of patients with tumors larger than 10 cm to have worse survival prognoses, this association did not show statistic significance.

Another example of a prognostic factor is the presence of calcifications in simple radiographs, which is reported to be present in about 15% to 20% of the cases.[1] In our study, the patients who presented with tumor calcifications did not have better survival prognoses. Nevertheless, Varela-Duran and Enzinger [29] [26] believed these calcifications to be a favorable prognostic factor. Their series showed 82% survival in cases presenting with heavy calcifications, better than all previously published papers.

Presence of mast cells also has been studied by some authors as a prognostic factor. It appears that mast cells have a positive influence on survival in SS cases. [27] [24] In our study, patients with tumors showing mast cells had better survival rates, ie, 11.0% versus 54.5%, but this difference was not statistically significant ($P = 0.07$).

More controversial potential prognostic factors include sex, age, type of treatment, and tumor location.

In summary, we observed a survival rate of 65% and a local recurrence rate of 15% in our study, which seems comparable to most studies published in the last decade concerning only SS. The unfavorable prognostic factors that influenced survival were spontaneous necrosis above 25%, proximal tumors, and high histologic grade according to our criteria. Local recurrence was higher only when the microscopic surgical margin was positive. Although our study is limited in terms of patient numbers, we believe, based on our results, that our criteria for determining high- and low-histologic grade SS are valid and have prognostic significance.

RESUMO

Baptista AM, Camargo OP de, Croci AT, Oliveira CRGCM de, Azevedo Neto RS de, Giannotti MA et al. Sarcoma sinovial das extremidades: fatores de prognóstico em 20 casos não-metastáticos e um novo sistema de graduação histológica com significado prognóstico. CLINICS. 2006;61(5):381-6.

OBJETIVO: Avaliar casos de sarcoma sinovial não-metastático das extremidades no que se refere a fatores prognósticos, e propor um sistema histológico de pontuação com significado prognóstico.

MATERIAL E MÉTODO: Vinte casos (14 do sexo feminino e 6 do sexo masculino) de sarcomas sinoviais não-metastáticos das extremidades tratados entre 1985 e 1998 no departamento de Ortopedia foram avaliados retrospectivamente no que se refere a fatores prognósticos e está sendo proposto um sistema de pontuação histológico com significado prognóstico.

RESULTADOS: A média dos períodos de acompanhamento foi 48,4 meses (mínimo 16 meses, máximo 116). Houve recorrência localizada em 3 casos (15%), sendo a margem cirúrgica microscópica o único fator prognóstico identificado. Sete pacientes (35%) morreram da doença, todos em período pós-operatório médio de 31,7 meses (mínimo 16 meses, máximo 53), todos com metástase pulmonar ou cerebral. A sobrevida foi de 65% em 48,4 meses de acompanhamento.

CONCLUSÃO: Os fatores prognósticos desfavoráveis identificados referentes à sobrevida foram: grau histológico alto, tumores proximais de joelho ou cotovelo e necrose espontânea de tumor acima de 25%. Neste estudo, a recorrência localizada não influiu na sobrevida. Parece que a presença de mastócitos influi positivamente na sobrevida, porém não obtivemos significado estatístico (p=0,07). O resultado

oncológico e funcional foi bom em seis casos (30%), regular em sete (35%) e insatisfatório em sete (35%).

UNITERMOS: Sarcoma sinovial. Extremidades. Estudos retrospectivos. Prognóstico. Neoplasmas em tecidos moles.

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